Robust Control of Yeast Fed-Batch Cultures for Productivity Enhancement

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Abstract: This work proposes a robust control strategy for the optimizing control of fed-batch cultures of S. cerevisae. The process dynamics is characterized by a nonlinear kinetic model based on the bottleneck assumption and ethanol inhibition for a possible excess of substrate feeding. The control strategy is based on the feedback linearization technique, where the resulting free linear dynamics is designed so as to ensure a certain robustness to plant parameter variations. A feedforward loop achieves the correct critical substrate value, which is a function of the ethanol and oxygen in the culture medium. In addition, a robust Luenberger-like observer is designed taking plant parameter variations into account. Numerical experiments demonstrate the potential of the proposed approach as a tool for control design of fed-batch cultures.

Keywords: robust control, feedback linearisation, Luenberger observer, fermentation process.

1. INTRODUCTION

The culture of host recombinant micro-organisms is probably the only economical way of producing pharmaceutical biochemicals. The cell cultures or the culture of micro-organisms are basically operated in three different modes – batch, fed-batch and continuous. The fed-batch operation is popular in industrial practice, because it is advantageous from an operational and control point of view (Roeva and Tzonkov, 2005). In this mode of operation, the bioreactor is manipulated by controlling its feeding rate. The off line design of the optimal feeding profile in general does not give high productivity, since in open-loop an excess of substrate leads to the accumulation of by-products (ethanol for yeast and acetate for bacteria), which in turn yields an inhibition of the cell respiratory capacity.

To avoid high concentrations of inhibitory by-product, a closed-loop solution is in general applied leading to a wide diversity of approaches (Chen et al., 1995; Boskovic and Narendra, 1995; Hisbullah et al., 2002; Rocha et al., 2004; Renard and Vande Wouwer, 2008; Ignatova et al., 2008). Nevertheless, the closed-loop control optimization of yeast fed-batch process is still a challenging task for two main reasons. Firstly, the process kinetics is governed by highly nonlinear functions with uncertain model parameters. Secondly, there is a lack of reliable and low cost online sensors for the measurement of key state variables.

In the control context, many researchers are applying online algorithms to cope with time-varying model uncertainties by either adaptive control (Renard and Vande Wouwer, 2008; Dewasme and Vande Wouwer, 2008; Ignatova et al., 2008) or computational intelligence based algorithms (Rocha et al., 2004; Karakuzu et al., 2006). However, the use of online adaption schemes may lead to closed-loop instability in the presence of unmodeled dynamics. In this paper, we follow a different direction by applying the robust control theory to design a nonlinear controller (with a fixed parametrization) taking model uncertainties into account. The control strategy is based on the classical feedback linearizing technique which is widely applied in fermentation process (Bastin and Dochain, 1990). However, feedback linearizing control schemes are very sensitive to model uncertainties. To handle the lack of robustness, the resulting linear dynamics is designed in order not only to improve the overall performance but also to achieve robustness against model uncertainties.

On the other hand, complex control methods need in general full state information which in most of the situations is not practical. In this case, many approaches have been proposed in the process control literature to estimate some unavailable key states based on Luenberger observer (LO) and Kalman filter (KF) (Bastin and Dochain, 1990; Klockow et al., 2008). However, these state estimators are implemented iteratively (e.g., extended LO and KF) to deal with the nonlinearities exhibited in the fermentation dynamics making difficult the task of tuning the observer gain in order to achieve a nice convergence behaviour. In this paper, we propose a robust nonlinear observer for which a nonlinear static gain is designed to improve the estimation convergence as well as to cope with model uncertainties. The rest of this paper is as follows. Section 2 introduces the problem to be addressed in this paper. The control strategy is proposed in Section 3 and the robust observer design is derived in Section 4. Numerical experiments are carried out in Section 5 to validate the approach and Section 6 ends the paper.

2. PRELIMINARIES

The yeast strain *S. cerevisiae* presents a metabolism that is macroscopically described as follows (Bastin and Dochain, 1990):

$$\text{Substrate oxidation:} \quad S + k_5 O \xrightarrow{r_1} k_1 X + k_7 P \tag{1}$$

$$\text{Substrate fermentation:} \quad S \xrightarrow{r_2} k_2 X + k_4 E + k_8 P \tag{2}$$

$$\text{Ethanol oxidation:} \quad E + k_6 O \xrightarrow{r_3} k_3 X + k_9 P \tag{3}$$

where X, S, E, O and P are, respectively, the concentration in the culture medium of biomass, substrate (typically glucose), ethanol, dissolved oxygen and carbon dioxide. The k_i, $i = 1, \ldots, 9$, are the constant yield coefficients and the r_i, $i = 1, 2, 3$, are the specific growth rates. We model these rates by the following discontinuous functions:

$$r_1 = \min\{r_S, k_5^{-1} r_O\} \tag{4}$$

$$r_2 = \max\{0, r_S - k_5^{-1} r_O\} \tag{5}$$

$$r_3 = \max\left\{0, \frac{r_O - k_5 r_S}{k_6} \cdot \frac{E}{E + K_E}\right\} \tag{6}$$

where the kinetic terms related to the substrate consumption r_S, the oxidative or respiratory capacity r_O and the ethanol oxidative rate r_E are represented as follows

$$r_S = \mu_S \, \frac{S}{S + K_S} \tag{7}$$

$$r_O = \mu_O \, \frac{O}{O + K_O} \cdot \frac{K_{i_E}}{K_{i_E} + E} \tag{8}$$

$$r_E = \mu_E \, \frac{E}{E + K_E} \tag{9}$$

with the constants μ_S, μ_O and μ_E being the maximal values of the specific growth rates and K_S, K_O and K_E expressing the saturation of the respective elements. Note that we are taking the effect of ethanol on the cells growth into account by considering the inhibition ethanol constant K_{i_E} in (8).

The component-wise mass balances of the above reaction scheme lead to the following state-space representation (Dewasme and Vande Wouwer, 2008)

$$\dot{x} = Kr(x)x_1 + Ax - ux + B(u) \tag{10}$$

where $x = [\, x_1 \; x_2 \; x_3 \; x_4 \; x_5 \; x_6 \,]' = [\, X \; S \; E \; O \; P \; V \,]'$ is the state vector with $x_6 = V$ being the culture medium volume, $r(x) = [\, r_1 \; r_2 \; r_3 \,]'$ is the vector of reaction rates, and $u = F_{in}/x_6$ is the control input (the dilution rate) with F_{in} denoting the inlet feed rate. The matrices K and A, and the vector function $B(\cdot)$ are given by:

$$K = \begin{bmatrix} k_1 & k_2 & k_3 \\ -1 & -1 & 0 \\ 0 & k_4 & -1 \\ -k_5 & 0 & -k_6 \\ k_7 & k_8 & k_9 \\ 0 & 0 & 0 \end{bmatrix}, \; B(u) = \begin{bmatrix} 0 \\ S_{in} \; u \\ 0 \\ k_L a \; O_{sat} \\ k_L a \; P_{sat} \\ 0 \end{bmatrix}, \tag{11}$$

$$A = \begin{bmatrix} 0_3 & 0_{3\times 2} & 0_{3\times 1} \\ 0 & -k_L a \; I_2 & 0 \\ 0_{1\times 3} & 0_{1\times 2} & 0 \end{bmatrix},$$

where $k_L a$ is the volumetric transfer coefficient, S_{in} is the feeding substrate concentration, and O_{sat} and P_{sat} are respectively the saturations of dissolved oxygen and carbon dioxide concentrations.

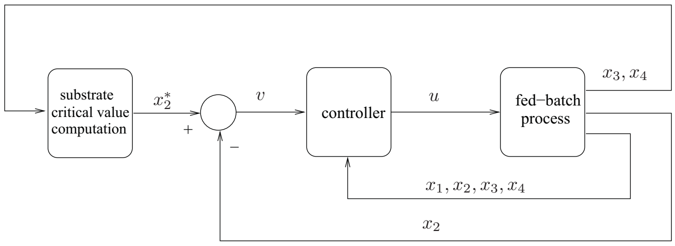

Fig. 1. Control Scheme for Optimal Operation Regime.

To analyze the biomass productivity, we recall the Sonnleitner's bottleneck assumption (Sonnleitner and Käppeli, 1986) which states that during a culture the yeast cells are likely to change their metabolism because of limited respiratory capacity. When the substrate concentration is large, the yeast cells produce ethanol (respiro-fermentative regime). If the substrate concentration becomes small, the available substrate (and possibly the ethanol) are oxidized (respirative regime). Thus, the optimal operating point to maximize the biomass productivity is at the boundary of the two regimes (Valentinotti et al., 2004), i.e., when the fermentation and oxidation reaction rates are equal to zero. Hence, the optimal operating point can be easily computed through the equality $r_O = k_5 r_S$ leading to the following equation

$$x_2^* = \frac{K_S \; r_O}{k_5 \mu_S - r_O} \tag{12}$$

where x_2^* refers to the substrate critical value.

In view of (8), we note that the operating point x_2^* is in fact a nonlinear function of x_3 and x_4. To simplify the control problem, many references either consider a constant set-point (Klockow et al., 2008) or alternatively choose a sub-optimal solution by imposing a low-level of ethanol concentration (Renard and Vande Wouwer, 2008).

3. CONTROL STRATEGY

In this paper, we aim at maintaining the system as close as possible to its optimal operating condition. To this end, we have to determine on-line the value of x_2^* and design a controller such that x_2 tracks approximately x_2^*. In addition, to simplify the analysis, we suppose in this section that all states are available on-line for feedback. For practical purposes, a nonlinear observer is proposed in the next section to estimate some state variables which are difficult to measure.

The proposed control scheme is illustrated in Figure 1. The internal feedback loops correspond to a standard feedback linearizing controller, where the free linear dynamics is designed to give a good tracking response as well as to assure a certain level of robustness against plant parameter variations. The external feedforward loop is to compute on-line the substrate critical level. We stress that instead of computing an adaptive controller to handle plant parameter variations (as, e.g., Dewasme and Vande Wouwer (2008)), we design a fixed controller that will have a guaranteed performance in the admissible parameter space.

To control the substrate level, consider the following dynamics for x_2 taken from (10)

$$\dot{x}_2 = -(r_1 + r_2)x_1 + (S_{in} - x_2)u \qquad (13)$$

where r_1 and r_2 are nonlinear functions of x_2, x_3 and x_4 as given by (4) and (5). With respect to the above system dynamics, we assume that the values of $x_1, \ldots, x_6$ are bounded to a given polytopic region $\mathcal{X}$ with know vertices, that is, $x \in \mathcal{X} \subset \mathbb{R}^6$.

A feedback linearizing control law can be easily derived:

$$u = \frac{F_{in}}{x_6} = \frac{1}{S_{in} - x_2}((\tilde{r}_1 + \tilde{r}_2)x_1 + v) \qquad (14)$$

where $\tilde{r}_1$ and $\tilde{r}_2$ are respectively the nominal values of r_1 and r_2, which may vary due to parameter variations, and v is the new input of the resulting linearized system.

In view of (13) and (14), we obtain the following dynamics for x_2

$$\dot{x}_2 = v - (e_{r_1} + e_{r_2})x_1 \qquad (15)$$

where $e_{r_1} := r_1 - \tilde{r}_1$ and $e_{r_2} := r_2 - \tilde{r}_2$ are nonlinear functions of (x_2, x_3, x_4) representing possible inexact cancelations of nonlinear terms due to uncertain model parameters.

Borrowing the ideas of the *Quasi-LPV* approach (Leith and Leithead, 2000), we bound the term $e_{r_1} + e_{r_2}$ by a time-varying parameter $\delta = \delta(t)$ which is supposed to belong to a known set $\Delta := \{\delta : \underline{\delta} \leq \delta \leq \overline{\delta}\}$ with $\underline{\delta}$ and $\overline{\delta}$ respectively representing the minimal and maximal admissible uncertainty.

To approximately track the time-varying reference signal x_2^*, we consider the following additional control loop

$$v = \lambda(x_2^* - x_2) \qquad (16)$$

where $\lambda \in \mathbb{R}$ is a free parameter to be designed.

In this paper, we design the parameter λ to ensure some robustness and a certain tracking performance to the overall closed loop system. To this end, we model the closed loop system as follows

$$\mathcal{M} : \begin{cases} \dot{x}_2 = -\lambda x_2 + a(\lambda, \delta)w \\ \quad z = -\, x_2 \, + \, c\, w \;,\; \delta \in \Delta \end{cases} \qquad (17)$$

where $w = [\, x_2^* \quad x_1\,]' \subset \mathcal{L}_{2,[0,T]}$ is a disturbance input to the system $\mathcal{M}$, $z = x_2^* - x_2$ the performance output and

$$a(\lambda, \delta) = [\, \lambda \quad -\delta \,] \;,\; c = [\, 1 \quad 0 \,] \;.$$

Now, consider the following definition for the finite horizon $\mathcal{L}_2$-gain of system $\mathcal{M}$:

$$\|\mathcal{M}_{wz}\|_{\infty,[0,T]} = \sup_{\delta \in \Delta, 0 \neq w \subset \mathcal{L}_{2,[0,T]}} \frac{\|z\|_{2,[0,T]}}{\|w\|_{2,[0,T]}} \qquad (18)$$

Thus, we design the parameter λ based on the $\mathcal{H}_\infty$ control theory (Skogestad and Postlethwaite, 2001). In other words, we solve the following optimization problem

$$\min_{\lambda, \delta \in \Delta} \gamma : \|\mathcal{M}_{wz}\|_{\infty,[0,T]} \leq \gamma \qquad (19)$$

while ensuring the robust stability of system (17).

Note 1. The parameter λ can be easily obtained through the LMI framework either via a quadratic Lyapunov function (Boyd et al., 1994) or a parameter dependent one (de Souza et al., 2000) if we assume $\dot{\delta}$ is also bounded, since we can easily perform a line search on λ. □

4. ROBUST OBSERVER

To implement the control law proposed in the latter section, we have to measure several state variables such as X, S, E and O. In spite of existing specific probes to measure all these signals on-line, some sensors can be quite expensive and are not always available in a practical set-up. Particularly, in the proposed control strategy, we are dealing with very low levels of substrate (glucose) and ethanol concentrations making their measurements expensive and inaccurate.

Alternatively, we propose a robust Luenberger-like nonlinear observer to estimate the substrate and ethanol concentration levels from the measurement of $x_1 = X$, $x_4 = O$, $x_5 = P$ and the dilution rate $u = F_{in}/x_6$. As we are dealing with a nonlinear system, the exponential observability property of the system is state dependent (Bastin and Dochain, 1990). In other words, for large estimation errors, the observer may diverge from the system operating point since the exponential observability is lost. To overcome this problem, we assume the initial conditions $x_2(0)$ and $x_3(0)$, which are respectively the initial substrate and ethanol concentration levels, are partially known (likely through inaccurate off-line measurements).

Firstly, we model the reaction rates by the following uncertain functions:

$$r_i(x) \cong r_i(\theta_i) = \alpha_i(1 + \beta_i\theta_i) \;,\; \theta_i \in [-1, 1] \qquad (20)$$

where, for $i = 1, 2, 3$, α_i is the steady-state value of r_i, θ_i is an uncertain time-varying parameter which models the displacement of r_i from its steady-state regime and also a possible inaccuracy on the system parameters, and β_i is a given constant added in light of the unitary normalization of the uncertain parameter space. Then, we propose the following state space representation for the observer

$$\begin{cases} \dot{\hat{x}} = K\hat{r}\hat{x}_1 + \hat{A}(u)\hat{x} + \hat{B}(u, y) + L(y, u)(y - \hat{y}) \\ \hat{y} = C_y\hat{x} \\ \hat{z} = C_z\hat{x} \end{cases} \qquad (21)$$

where $\hat{x} \in \mathbb{R}^6$ is the state estimation, $y = C_y x$ is the on-line measurement, $\hat{y}$ is the measurement estimation, $\hat{z}$ is the signal to be estimate, K is as in (11), $L(y, u) \in \mathbb{R}^{6\times4}$ is a nonlinear matrix function of y and u to be determined, $\hat{r}$ is as defined in (24), and

$$\hat{A}(u) = -\mathrm{diag}\{0, u, u, k_La, k_La, 0\}$$
$$\hat{B}(u, y) = [\, -x_1u \quad S_{in}u \quad 0 \quad (k_LaO_{sat} - x_4u) \quad (k_LaP_{sat} - x_5u) \quad -x_6u \,]' \qquad (22)$$
$$C_y = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix} \;,\; C_z = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \end{bmatrix} \;.$$

Accordingly to (20), we define the estimates of $r_i(\theta_i)$ as follows

$$\hat{r}_i := \alpha_i \qquad (23)$$

where, for $i = 1, 2, 3$, $\hat{r}_i$ is the estimate of the approximate reaction rates.

Now, considering the following notation

$$r(\theta) = \begin{bmatrix} \alpha_1(1+\beta_1\theta_1) \\ \alpha_2(1+\beta_2\theta_2) \\ \alpha_3(1+\beta_3\theta_3) \end{bmatrix} \;,\; \theta = \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \end{bmatrix} \;,\; \hat{r} = \begin{bmatrix} \alpha_1 \\ \alpha_2 \\ \alpha_3 \end{bmatrix} \;, \qquad (24)$$

we can approximate the error dynamics as follows

$$\begin{aligned}\dot{e} &\cong (K\hat{r}N_r + \hat{A}(u) - L(y,u)C_y)e + K(r(\theta) - \hat{r})x_1 \\ &\cong (K\hat{r}N_r + \hat{A}(u) - L(y,u)C_y)e + K\Omega(x_1)\theta\end{aligned}$$

where $N_r = [\,1\ 0\ \cdots\ 0\,]$, $\theta \in \Theta := \{\theta \in \mathbb{R}^3 : |\theta_i| \le 1\ ,\ i = 1,2,3\}$ and $\Omega(x_1) = x_1 \cdot \mathrm{diag}\{\alpha_1\beta_1, \alpha_2\beta_2, \alpha_3\beta_3\}$.

In light of the above developments, we can pose the problem of determining $L(y,u)$ in an ℓ_1 optimal control setting (Dahleh and Diaz-Bobillo, 1995). To this end, consider the following error dynamics representation:

$$\mathcal{E} : \begin{cases} \dot{e} &= A_e e + B_e \theta \\ z_e &= C_z e\ ,\ \|\theta\|_\infty \le 1 \end{cases} \tag{25}$$

where θ is an energy-peak bounded disturbance signal, z_e the estimation error to be minimized and

$$A_e = K\hat{r}N_r + \hat{A}(u) - L(y,u)C_y\ ,\ B_e = K\Omega(x_1)\ .$$

In this paper, we consider the following definition for the ℓ_1-norm of system (25):

$$\|\mathcal{E}_{\theta z_e}\|_1 = \sup_{\substack{e \in \mathbb{E}, e(0) = 0 \\ \|\theta\|_\infty \le 1}} \|z_e\|_\infty \tag{26}$$

where $\mathbb{E} := \{e : V(e) \le 1\}$ is an estimate of the reachable set and $V(e)$ is a Lyapunov function for system $\mathcal{E}$, which guarantees the system internal stability.

An upper-bound σ on $\|\mathcal{E}_{\theta\ e_z}\|_1^2$ can be determined via the following optimization problem (Nagpal et al., 1994)

$$\min_{\substack{V(e),\eta \\ e \in \mathbb{E}}} \ \sigma : \begin{cases} V(e) > 0\ ,\ \eta > 0 \\ \dot{V}(e) + \eta(V(e) - \theta'\theta) < 0 \\ V(e) - \dfrac{z_e' z_e}{\sigma} \ge 0 \end{cases} \tag{27}$$

Notice the set invariance property of $\mathbb{E}$ is guaranteed for zero initial conditions and the constraints on (27) may not hold when $e(0) \neq 0$. As a result, the error state trajectory may leave $\mathbb{E}$ and do not return since the state observer is nonlinear and the stability properties are not necessarily global. In this paper, we assume the initial error is sufficiently close to zero such that $\mathbb{E}$ is attractive.

5. NUMERICAL EXPERIMENTS

In this section, we perform several numerical experiments considering small-scale culture conditions. In particular, we borrow the 20 $[l]$ bioreactor studied in (Dewasme and Vande Wouwer, 2008), where the initial and operating conditions are:

$$x_1(0) = 0.4\ [g/l]\ ,\ x_2(0) = 0.5\ [g/l]\ ,\ x_3(0) = 3\ [g/l]\ ,$$
$$x_4(0) = O_{sat} = 0.035\ [g/l]\ ,\ x_5(0) = P_{sat} = 1.286\ [g/l]\ ,$$
$$x_6(0) = 6.8\ [l] \quad \text{and} \quad S_{in} = 350\ [g/l]\ .$$

We study two different scenarios. Firstly, supposing the state variables are available online for feedback, we design the robust linearizing feedback controller proposed in Section 3 aiming for tracking as close as possible the estimation of the substrate critical value. In this setup, we consider a noisy ethanol measurement, since the level of ethanol is likely to be very close to zero making difficult its measurement. Secondly, we design a robust observer to estimate the substrate and ethanol concentration levels, which in the proposed strategy are very low and difficult to measure in current practice, applying the result proposed in Section 4. In this case, we analyze the observer robustness and verify the set of initial conditions in which the convergence properties hold.

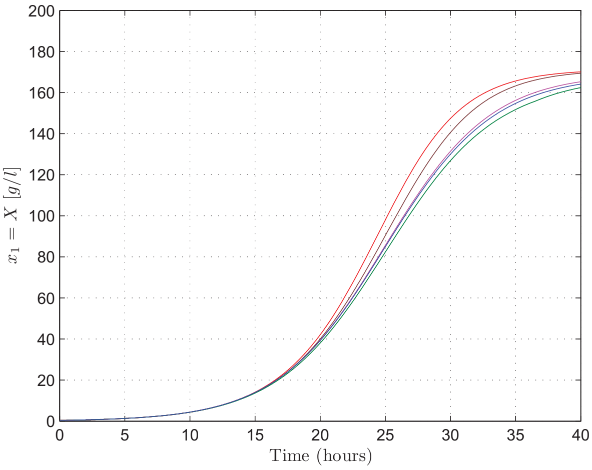

Fig. 2. Biomass concentration – state feedback case.

5.1 State Feedback

We refer to state feedback the control law proposed in (14) and (16), where x_1, x_2, x_3, x_4 and u are available online. To design the parameter λ in (16) via the optimization problem (19), we suppose the parameters K_S, K_E, K_O and K_{i_E} may vary $\pm 20\%$ from their nominal values. Simulating the operating conditions of the control strategy in (14), we may infer that $\overline{\delta} = -\underline{\delta} = 1.0$, which in light of (17) and (19) yields $\lambda = 44.8511$.

Figures 2 to 4 show the closed-loop response of biomass x_1, substrate x_2 and ethanol x_3 concentrations, for five different values of K_S, K_E, K_O and K_{i_E} (which were randomly chosen). In all simulations, we have added a white noise on the ethanol concentration measurement with a maximal amplitude of $\pm 0.25\ [g/l]$. Notice in all cases the biomass productivity does not significantly vary against parameter uncertainty and noise measurement.

5.2 Output Feedback

In order to design the state observer as proposed in Section 4, we have considered

$$\alpha_1 = 3.2 \times 10^{-5}\ ,\ \alpha_2 = 1.3 \times 10^{-6}\ ,\ \alpha_3 = 4 \times 10^{-7}\ ,$$
$$\beta_1 = \beta_2 = \beta_3 = 1\ ,\ x_1 \in [0.4, 180]\ ,\ F_{in} \in [10^{-7}, 10^{-4}]\ ,$$

which are obtained from the noiseless simulations of the state-feedback case.

We can compute the observer gain through the LMI framework, see for instance (Coutinho et al., 2005). Assuming that u is available online, we have chosen an observer gain as follows:

$$L(y,u) = L(u) = L_0 + uL_1\ ,$$

where L_0 and L_1 are constant matrices to be determined. In addition, to simplify the computations, we constraint the Lyapunov function to be quadratic, i.e., $V(e) = e'Pe$ with $P = P' > 0$.

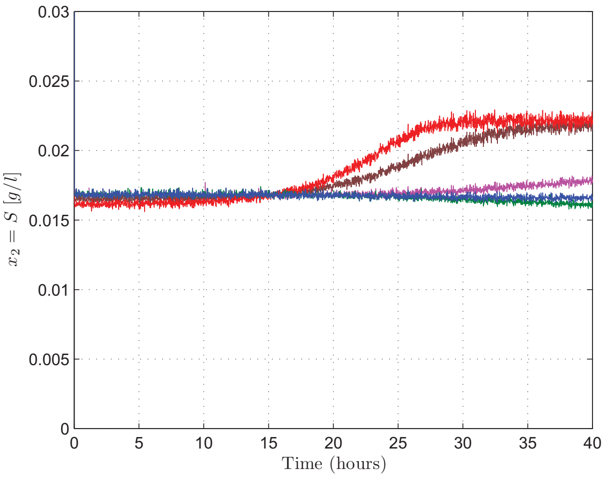

Fig. 3. Substrate concentration – state feedback case.

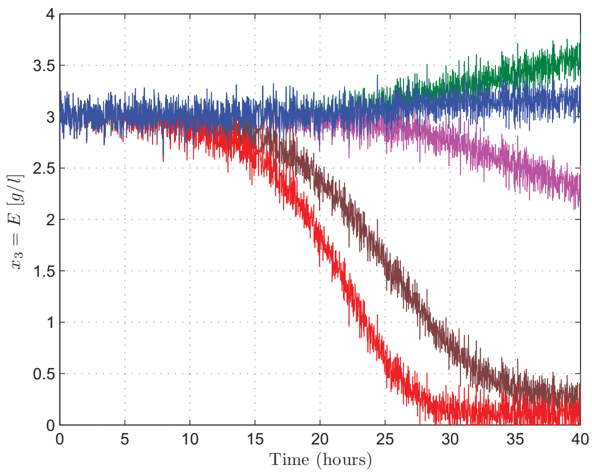

Fig. 4. Ethanol concentration – state feedback case.

Thus, solving (27) for all $(x_1, u) \in \mathcal{V}([0.4, 180] \times [10^{-7}, 10^{-4}])$ with the parametrization $Q(u) = PL(u)$ and a line search on η, we obtain the following matrices

$$L_0 = 10^6 \times \begin{bmatrix} 0.267 & -0.380 & 1.006 & 0.000 \\ -0.208 & 1.421 & -3.759 & 0.000 \\ 0.058 & -0.341 & 0.903 & 0.000 \\ -0.041 & 0.283 & -0.747 & 0.000 \\ 0.109 & -0.747 & 1.978 & 0.000 \\ 0.000 & 0.000 & 0.000 & -2\times 10^{-7} \end{bmatrix}$$

$$L_1 = 10^2 \times \begin{bmatrix} 0.143 & -0.256 & 0.679 & 0.000 \\ -0.172 & 1.217 & -3.220 & 0.000 \\ 0.045 & -0.290 & 0.768 & 0.000 \\ -0.034 & 0.241 & -0.639 & 0.000 \\ 0.090 & -0.639 & 1.690 & 0.000 \\ 0.000 & 0.000 & 0.000 & 0.000 \end{bmatrix}$$

where $\mathcal{V}(\cdot)$ stands for the set of vertices of $(\cdot)$.

From several simulations, the observer initial conditions that guarantee the stability of the error system are as follows

$$\hat{x}_2(0) = x_2(0) \pm 50\% \ , \ \hat{x}_3(0) = x_3(0) \pm 50\% \ . \qquad (28)$$

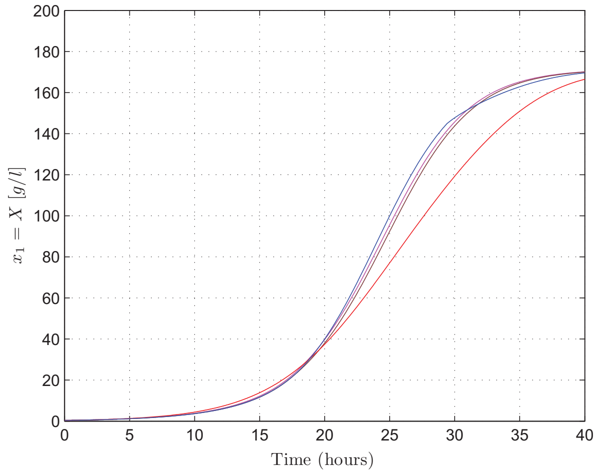

Fig. 5. Biomass concentration – output feedback case.

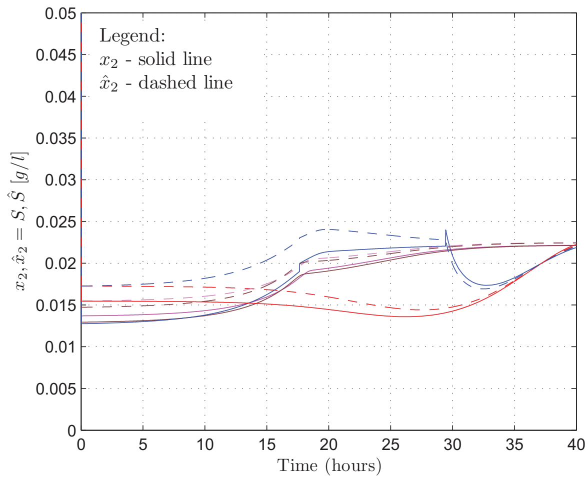

Fig. 6. Substrate concentration – output feedback case.

To test the output feedback closed-loop performance, we carried out several simulations for randomly chosen values of K_S, K_E, K_O, K_{i_E} and $\hat{x}_2(0), \hat{x}_3(0)$ from the admissible parameter space leading to the results detailed in Figures 5, 6 and 7.

5.3 Remarks and Future Research

The simulations indicate that the overall performance of the biomass concentration productivity is robust against uncertainties on model parameters and some initial condition estimates. The biomass productivity is similar to the one obtained in (Dewasme and Vande Wouwer, 2008), where an adaptive control is applied for a similar setup, but the proposed approach achieved a better transient performance. However, the ethanol concentration level does not always converge to zero indicating an error on the estimation of x_2^*. Notice we determine x_2^* from (12) which is a function of some partially known parameters. Further developments are needed to improve the estimation of the substrate concentration critical level.

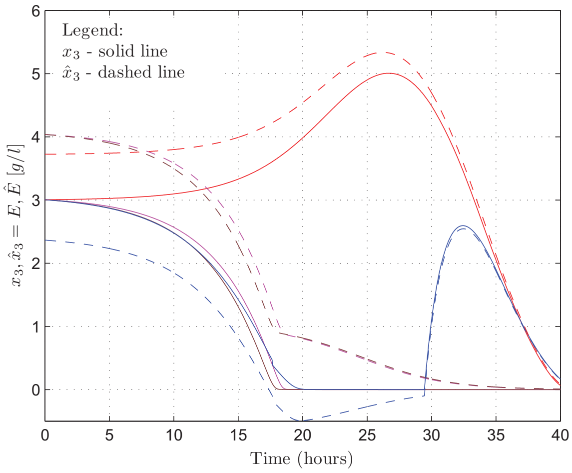

Fig. 7. Ethanol concentration – output feedback case.

6. CONCLUSION

This paper has proposed a robust control strategy to optimize the production of yeast cultures in fed-batch operation. Firstly, assuming full state information, a robust controller is designed for ensuring a guaranteed performance in spite of parameter uncertainty. Then, a nonlinear robust observer is derived in order to estimate the states that are not available online for feedback. Numerical examples have demonstrated the applicability of the proposed approach to control yeast fed-batch fermentation processes.

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